

REMARKS

Claims 1, 2, 5-15, 18-22 and 56-62 are present in the application and stand rejected. By the foregoing amendments, Claims 1, 56, 58 and 60-62 have been amended to correct a clerical error, to delete the term "TRIZMA Base" which is a trademark and redundant and unnecessary in view of the generic term tris (hydroxymethyl) aminomethane, and to require that the chelating agent is present in the composition at a concentration in the range of 0.1 mM to 100.0 mM. Support for the latter amendment is found *inter alia* at page 20, lines 3-5, of the application as filed. In view of the foregoing claim amendments and arguments that follow, applicants submit that all of the pending claims are in condition for allowance. A Request for Continued Examination is submitted herewith. Reconsideration and favorable action is requested.

Rejection of Claims 1, 2, 5, 7, 8, 12-15, 18-22 and 56-62 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 2, 5, 7, 8, 12-15, 18-22 and 56-62 under 35 U.S.C. § 103(a) as being unpatentable over Raad et al. (U.S. Patent No. 6,165,484, hereafter the '484 Patent) and Cuny et al. (U.S. Patent No. 6,207,679, hereafter the '679 Patent). This rejection is respectfully traversed.

Representative Claim 1 of the present application is directed to methods of inhibiting proliferation of a *bacterial population* of a skin injury or surface lesion of a human or animal patient by contacting the surface (i.e., topical application) of the skin injury or the surface lesion with an antibacterial composition of:

- a pharmaceutically acceptable antibacterial agent
- a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA) at a concentration in the range of 0.1 mM to 100.0 mM
- tris (hydroxymethyl) aminomethane, and
- a pharmaceutically acceptable carrier

The chelating agent and the antibacterial agent are present in the composition at concentrations selected to allow synergistic cooperation between said antibacterial agent and said chelating agent to inhibit proliferation of the bacterial population of the skin injury or the surface lesion of the human or animal patient. In practice, the compositions of the invention are delivered to the surface of the skin injury or the surface lesion of the patient, such as by incorporating the compositions in a medical dressing.

In rejecting the applicants' claims, the Examiner has cited the Raad et al. '484 patent as teaching "treating bacterial and fungal infections topically by applying a composition comprising antibacterial/fungal agents working synergistically with chelating agents such as EDTA and active agents such as amphotericin" It is respectfully submitted that the Examiner's characterization of the Raad et al. '484 patent is in error.

The '484 Patent is Directed to the Treatment of *Systemic Fungal Infections* not Bacterial Infections

The Raad et al. '484 patent is directed to the systemic treatment of fungal infections, not to treating "bacterial and fungal infections topically" as suggested by the Examiner. As stated by the Raad et al. '484 patent at Column 2, lines 5-10:

The present invention provides an effective method of treating a systemic fungal infection comprising the steps of obtaining a therapeutically effective amount of a pharmaceutical composition comprising at least one chelator, at least one antifungal agent and a pharmaceutical excipient, diluent or adjuvant, and administering said pharmaceutical composition to a patient having a fungal infection. [Emphasis added.]

The Raad et al. '484 patent further states at Column 7, line 52, through Column 8, line 3:

The present invention provides pharmaceutical compositions and methods for the prevention and treatment of disseminated fungal infections. It is contemplated that the preparations of the invention will be useful in eliminating or inhibiting all types of fungal infections, providing so-called fungicidal or fungistatic effects. For example, the inventors have discovered that chelators have significant growth inhibitory effect against species of *Aspergillus* (see data in FIG. 1, FIG. 2, FIG. 3 and FIG. 4). The inventors have further demonstrated conclusively and unexpectedly that,

when combined with antifungal agents, chelators show additive to synergistic inhibitory activity against the growth of fungal pathogens (see data in FIG. 5, FIG. 6, FIG. 7, FIG. 8, FIG. 9, FIG. 10 and FIG. 11). These discoveries provide the basis for a program of prevention and treatment of systemic fungal infections using any of several embodiments of the inventive pharmaceutical formulations, which may comprise various combinations of chelators, antifungal agents, and any necessary excipients, diluents or adjuvants. [Emphasis added.]

The Raad et al. '484 patent further states at Column 15, lines 13-26:

The inventors have demonstrated, remarkably and for the first time, that the chelators and antifungal agents of the present invention act together in a synergistic fashion to inhibit fungal pathogens. It is contemplated that as a consequence of this synergism described above between the chelators and the antifungal agents of the present invention, decreased dosages of antifungal agent will be sufficient to induce a fungicidal effect in a patient with a fungal infection, relative to the dosage required when administering an antifungal agent alone. Advantageously, a decreased dosage of antifungal agent, when used in conjunction with the chelators of the present invention, will serve to minimize any undesirable side effects which antifungal agents may induce in patients to whom they are administered.

In fact, the entire invention of the Raad et al. '484 patent is directed to the treatment of fungal infections with antifungal agents and chelators, and NOT to the treatment of bacterial infections with antibacterial agents, as suggested by the Examiner.

The Examiner has specifically referred to the Raad et al. '484 patent's disclosure of the antifungal agent amphotericin. Amphotericins, such as amphotericin B, are polyene antimycotic drugs primarily used intravenously in the treatment of systemic fungal infections. As disclosed in the Raad et al. '484 patent at Column 14, lines 36-40, "The polyenes bind to ergosterols in fungal membranes, resulting in the formation of transmembrane channels which allow the escape of metabolites essential to maintaining the viability of the fungal cell." As further disclosed at Column 14, lines 58-63, "Antifungal agents particularly preferred in connection with the present invention include the polyenes, most preferably Amphotericin B and liposomal Amphotericin B. The inventors have demonstrated that Amphotericin B acts synergistically in concert with the chelator EDTA to inhibit species of *Aspergillus* and *Fusarium*." A polyene is a circular molecule

consisting of a hydrophobic and hydrophilic region (i.e., an amphoteric molecule). The polyene antimycotics bind with sterols (e.g., principally ergosterol) present in the fungal cell membrane, changing the transition temperature (T_m) of the cell membrane from a fluid to a more crystalline state. As a result, the cell's contents leak out and the cell dies (usually the hydrophilic contents). Due to significant differences between eukaryotic fungal cells and prokaryotic bacterial cells, bacteria are largely resistant to amphotericin B and related antifungals, such as nystatin, natamycin and ketoconazole.

Contrary to the position relied upon by the Examiner, fungi are not bacteria and due to substantial differences in cell structure and composition, entirely different classes of drugs having differing chemical structures and mechanisms of action have evolved for the inhibition of each. The disclosure of the Raad et al. '484 patent is specifically directed to a synergistic combination of antifungal agents and chelators, and particularly to the polyene antifungal agents amphotericin B, nystatin, natamycin, liposomal amphotericin B, and liposomal nystatin, together with EDTA. There is no disclosure or remote suggestion in the Raad et al. '484 patent that the action of other classes of drugs could be synergistically enhanced in combination with a chelating agent. A person of ordinary skill in the art could not possibly arrive at that conclusion from the disclosure of the Raad et al. '484 patent.

In addition, there is no disclosure or remote suggestion in the '484 patent of inhibiting the proliferation of a bacterial population of a skin injury or surface lesion by topically applying an antibacterial composition of (1) a pharmaceutically acceptable antibacterial agent, (2) a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriaminopentaacetic acid (DPTA), (3) tris (hydroxymethyl) aminomethane, and (4) a pharmaceutically acceptable carrier, where the antibacterial agent and the chelating agent are present in concentrations allowing synergistic cooperation between the antibacterial agent and the chelating agent to inhibit proliferation of the bacterial population of the skin injury or the surface lesion of a human or animal patient, as required by the claims of the present application.

The '679 Patent Does Not Disclose or Suggest the Claimed Invention

The Examiner has cited the Cuny et al. '679 patent as teaching the use of antimicrobial agents in the treatment of infections in wounds, for topical treatment and for efficacy against gram-positive and negative bacteria.

The Cuny et al. '679 patent is directed to new antibacterial compounds – a specifically disclosed family of 2-(3-indolyl)-4-quinolinocarboxamide compounds and their substituted derivatives. Although the Cuny et al. '679 patent contains a generic disclosure of virtually all pharmaceutically acceptable routes of administration of the compounds and does indicate that a virtual laundry list of additional components including wetting agents, emulsifiers and lubricants, coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants (including EDTA) can also be present in compositions of the new family of compounds, there is no disclosure or remote suggestion of topically administering a composition comprising synergistic concentrations of a pharmaceutically acceptable antibacterial agent and a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), together with tris (hydroxymethyl) aminomethane, and a pharmaceutically acceptable carrier, as required by applicants' amended claims. Accordingly, the Cuny et al. '679 patent does not overcome the deficiencies of the Raad et al. '484 patent.

The Cuny et al. '679 Patent Cannot Be Combined With the Raad et al. '484 Patent In Rejecting Applicants' Claims

In rejecting applicants' claims, the Examiner has stated that:

[O]ne of ordinary skill in the art would have been motivated to follow the teachings of '679 to combine biocidal compounds such as those found in both '679 and '484 in order to treat Gram-positive or negative bacterial infections. The '484 [sic] teaches the importance of synergistic relationship between the chelators and the biocide, while the '679 [sic] teaches the varying methods of application

However, as set forth in detail above, the Raad et al. '484 patent clearly does not disclose, suggest or imply a broad synergistic relationship between chelators and all biocides. Rather, the

disclosure of the Raad et al. '484 patent is specifically limited to a synergistic combination of antifungal agents and chelators, and particularly to the polyene antifungal agents amphotericin B, nystatin, natamycin, liposomal amphotericin B, and liposomal nystatin, together with EDTA. In addition, there is no motivation or suggestion to combine the teachings of the '679 patent with those of the '484 patent in the manner applied by the Examiner, but rather such combination appears to have been made with the hindsight benefit of applicants' disclosure and claims, which is highly inappropriate.

As set forth above, the Raad et al. '484 patent is directed to the systemic treatment of fungal infections, not to treating "bacterial and fungal infections" as suggested by the Examiner. In describing its discovery of the synergistic mechanism of action of antifungal agents and chelators, the Raad et al. '484 patent states at Column 8, lines 31-49:

It is known that iron and other trace metals are essential in the life cycle of microorganisms such as fungi. Without these trace metals, fungi are unable to grow and reproduce. Although iron is abundant in nature, its availability for microbial assimilation is limited owing to the insolubility of ferric ions at neutral or alkaline pH. *As a consequence, many fungi have evolved their own specialized trace metal-scavenging molecules, called siderophores, which bind with trace metals and make them available for uptake by the fungi. The chelators used in conjunction with the present invention provide an inhibitory effect upon fungal pathogens by competing with the fungal siderophores for any available trace metal ions.* In this way, the chelators present in the pharmaceutical preparations of the invention "steal" the metal ions essential for fungal growth, effectively causing the fungus to "starve to death." The added antifungal agents and/or monoclonal antibodies of the preparations of the invention can then come in and attack the weakened fungi, thereby destroying them or inhibiting their growth.

Since the entire mechanism of action disclosed in the Raad et al. '484 patent for synergistic interaction between its antifungal agents and chelators is dependent on fungi's "own specialized trace metal-scavenging molecules, called siderophores, which bind with trace metals and make them available for uptake by the fungi", there is no basis whatsoever for motivating any person of ordinary skill in the art to combine the teachings of the Raad et al. '484 patent with

any reference (including the Cuny et al. '679 patent) dealing with non-fungal infections. Accordingly, the Raad et al. '484 patent teaches directly away from the combination of references cited by the Examiner.

In addition, the Cuny et al. '679 patent cites ethylene diamine tetracetic acid as an optional antioxidant (see the '679 patent at Column 38, lines 5-20), not as a required, synergistically acting chelating agent as set forth in the claims of the present application.

Finally, even if combined, the combination of the '484 patent with the '679 patent does not disclose or suggest the combination of an antibacterial agent, a chelating agent, tris (hydroxymethyl) amino methane, and a pharmaceutically acceptable carrier as required by applicants' amended claims.

In view of the foregoing, it is believed that the Examiner's rejection of claims 1, 2, 5, 7, 8, 12-15, 18-22 and 56-62 under 35 U.S.C. § 103(a) over the combined disclosures of the Raad et al. '484 patent and the Cuny et al. '679 patent should properly be withdrawn.

Rejection of Claims 6 and 9 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 6 and 9 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the '484 patent, the '679 patent, and Raad et al. (U.S. Patent No. 5,688,516, hereafter the '516 patent). Claim 6 is directed to the method of Claim 1, wherein the pharmaceutically acceptable chelating agent is triethylene tetramine dihydrochloride (TRIEN). Claim 9 is directed to the method of Claim 1, wherein the pharmaceutically acceptable antibacterial agent is oxytetracycline. The Examiner has cited the Raad et al. '516 patent as disclosing a method of treating Gram positive and negative bacterial infections by applying a composition of chelating agents such as EDTA and triethylene tetramine dihydrochloride and various anti-bacterial agents including oxytetracycline. In this rejection, the Examiner has stated "one of ordinary skill in the art would have been motivated to combine the compounds of the '516 patent into the combination of '679 and '484 in order to treat a wider range of bacterial infections."

As set forth above, the Raad et al. '484 patent and the Cuny et al. '679 patent have been improperly combined by the Examiner and, even if combined, fail to disclose or suggest applicants' claimed invention. The Raad et al. '516 patent does not disclose or suggest either synergistic combinations of antibacterial agents and chelating agents, or the specific compositions of applicants' claimed invention, and does nothing to overcome the basic deficiencies of the Raad et al. '484 patent and the Cuny et al. '679 patent. Applicants' Claims 6 and 9 would not be obvious to any person of ordinary skill in the art within the meaning of 35 U.S.C. § 103(a) over this combination of references. It is believed that the Examiner's rejection of Claims 6 and 9 should properly be withdrawn.

Rejection of Claims 10 and 11 Under 35 U.S.C. § 103(a) as Being Unpatentable Over the Combined Disclosures of the '484 Patent, the '679 Patent, and Kruse et al. (U.S. Patent No. 5,646,151 (Hereafter the '151 Patent))

The Examiner has rejected Claims 10 and 11 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the '484 patent, the '679 patent, and Kruse et al. (U.S. Patent No. 5,646,151, hereafter the '151 patent). Claim 10 is directed to the method of Claim 1, wherein the pharmaceutically acceptable antibacterial agent is amikacin. Claim 11 is directed to the method of Claim 1, wherein the pharmaceutically acceptable antibacterial agent is neomycin. The Examiner has cited the Kruse et al. '151 patent as disclosing topical formulations comprising chelating agents such as EDTA and antibiotic agents such as neomycin, amikacin and tetracyclines. In this rejection, the Examiner has stated, "one of ordinary skill in the art would have been motivated to combine the compounds of the '151 patent into the combination of '679 and '484 in order to treat a wider range of bacterial infections."

As set forth above, the Raad et al. '484 patent and the Cuny et al. '679 patent have been improperly combined by the Examiner and, even if combined, fail to disclose or suggest applicants' claimed invention. The Kruse et al. '151 patent does not disclose or suggest either synergistic combinations of antibacterial agents and chelating agents, or the specific

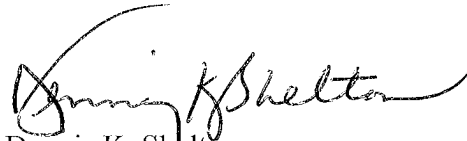
compositions of applicants' claimed invention, and does nothing to overcome the basic deficiencies of the Raad et al. '484 patent and the Cuny et al. '679 patent. Applicants' Claims 10 and 11 would not be obvious to any person of ordinary skill in the art within the meaning of 35 U.S.C. § 103(a) over this combination of references. It is believed that the Examiner's rejection of Claims 10 and 11 should properly be withdrawn.

CONCLUSION

In view of the foregoing claim amendments and arguments, applicants respectfully submit that Claims 1, 2, 5-15, 18-22 and 56-62 are in condition for allowance. Reconsideration and favorable action are requested. The Examiner is further requested to contact applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

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